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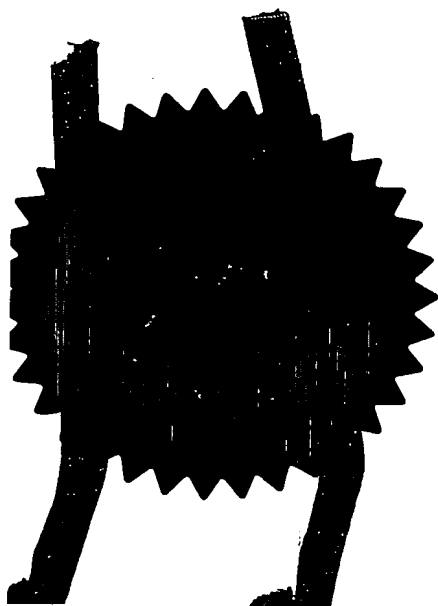
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Patents Form 1/77

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30MAY03 1810594-1/000029  
P01/7700 1.00-0312296.7

Request for grant of a patent

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29 MAY 2003

The Patent Office

Cardiff Road  
Newport  
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1. Your reference **P034325GB**

2. Patent application number  
(The Patent Office will fill in this part) **0312296.7**

3. Full name, address and postcode of the or of each applicant (underline all surnames)

**RIBOTARGETS LIMITED**  
Granta Park  
Abington  
Cambridge  
CB1 6GB

Patents ADP number (if you know it)

**7800113001**

If the applicant is a corporate body, give the country/state of its incorporation

**UNITED KINGDOM**

4. Title of the invention **PYRAZOLO-PYRIMIDINE COMPOUNDS AND THEIR USE IN MEDICINE**

5. Name of your agent (if you have one)

"Address for service" in the United Kingdom to which all correspondence should be sent (including the postcode)

**Carpmaels & Ransford**  
43 Bloomsbury Square  
London  
WC1A 2RA

Patents ADP number (if you know it)

**83001** ✓

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and (if you know it) the or each application number	Country	Priority application number (if you know it)	Date of filing (day / month / year)

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application	Number of earlier application	Date of filing (day / month / year)

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? (Answer 'Yes' if:

a) any applicant named in part 3 is not an inventor, or

b) there is an inventor who is not named as an applicant, or

c) any named applicant is a corporate body

Yes

See note (d))

## Patents Form 1/77

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Continuation sheets of this form

Description

29 ✓

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Claim(s)

5 ✓

Abstract

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Priority documents

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Statement of inventorship and right to grant of a patent (*Patents Form 7/77*)

Request for preliminary examination and search (*Patents Form 9/77*)

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11. I/We request the grant of a patent on the basis of this application.

Signature

*Carpmael - Ransford*  
Carpmaels & Ransford

Date

29th May 2003

12. Name and daytime telephone number of person to contact in the United Kingdom

P.N. HOWARD

020-7242 8692

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## **Pyrazolo-pyrimidine Compounds and their Use in Medicine**

This invention relates to the use of a class of substituted amino pyrazolo[1,5-a]pyrimidines in relation to diseases which are mediated by excessive or inappropriate CDK2 activity, such as cancers.

### Background to the invention

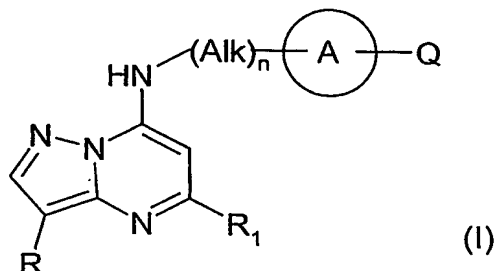
Uncontrolled cell proliferation is a hallmark of cancer. Tumor cells typically have damage to genes which play a part in regulation of the cell division cycle. Cyclin-dependent kinases (CDKs) play critical roles in regulating the transitions between different phases of the cell cycle. The serine/threonine kinase CDK2 is essential for normal cell cycling and plays a key role in disorders arising from aberrant cell cycling. Inhibitors of CDK2 are therefore useful for the treatment of various types of cancer and other conditions related to abnormal cell proliferation. Flavopyridol (M.D. Losiewicz et al., Biochem. Biophys. Res. Commun., 1994, 201, 589-595), which is currently in clinical trials, displays modest selectivity for inhibition of CDKs over other kinases but inhibits CDK1, CDK2, and CDK4 with equal potency. A purine based derivative, roscovitine (CYC-202) (W.F. De Azevedo et al., Eur. J. Biochem., 1997, 243, 518-526), similarly displays selectivity for CDKs over other kinases and is also in clinical trials.

### Brief description of the invention

The present invention relates to the use of a class of amino pyrazolo[1,5-a]pyrimidine compounds as CDK2 inhibitors, for example for inhibition of cancer cell proliferation. A core 7-amino pyrazolo[1,5-a]pyrimidine ring with aromatic substitution on the amino group are principle characterising features of the compounds with which the invention is concerned.

### Detailed description of the invention

According to the present invention there is provided the use of a compound of formula (I) or a salt, N-oxide, hydrate or solvate thereof, in the preparation of a composition for inhibition of CDK2 activity:



wherein

Ring A is optionally substituted aryl or heteroaryl,

Alk represents an optionally substituted divalent C<sub>1</sub>-C<sub>6</sub> alkylene radical;

n is 0 or 1;

Q represents a radical of formula  $-(\text{Alk}^1)_p-(\text{X})_r-(\text{Alk}^2)_s-\text{Z}$  wherein in any compatible combination

Z is hydrogen or an optionally substituted carbocyclic or heterocyclic ring,

Alk<sup>1</sup> and Alk<sup>2</sup> are optionally substituted divalent C<sub>1</sub>-C<sub>6</sub> alkylene radicals,

X represents -O-, -S-, -(C=O)-, -(C=S)-, -SO<sub>2</sub>-, -SO-, -C(=O)O-, -OC(=O)-, -C(=O)NR<sup>A</sup>-, -NR<sup>A</sup>C(=O)-, -C(=S)NR<sup>A</sup>-, -NR<sup>A</sup>C(=S)-, -SO<sub>2</sub>NR<sup>A</sup>-, -NR<sup>A</sup>SO<sub>2</sub>-, -OC(=O)NR<sup>A</sup>-, -NR<sup>A</sup>C(=O)O-, or -NR<sup>A</sup>- wherein R<sup>A</sup> is hydrogen or C<sub>1</sub>-C<sub>6</sub> alkyl,

p, r and s are independently 0 or 1, and

R<sub>1</sub> represents a radical  $-(\text{Alk}^3)_a-(\text{Y})_b-(\text{Alk}^4)_d-\text{B}$  wherein

a, b and d are independently 0 or 1,

Alk<sup>3</sup> and Alk<sup>4</sup> are optionally substituted divalent C<sub>1</sub>-C<sub>3</sub> alkylene radicals,

Y represents -O-, -S-, or -NR<sup>A</sup>- wherein R<sup>A</sup> is hydrogen or C<sub>1</sub>-C<sub>6</sub> alkyl,

B represents hydrogen or halo, or an optionally substituted monocyclic carbocyclic or heterocyclic ring with 5 or 6 ring members, or in the case where Y is -NR<sup>A</sup>- and b is 1, then R<sup>A</sup> and the radical -(Alk<sup>4</sup>)<sub>d</sub>-B taken together with the nitrogen to which they are attached may form an optionally substituted heterocyclic ring,

R represents hydrogen, bromo, C<sub>1</sub>-C<sub>6</sub> alkyl, phenyl, benzyl, cycloalkyl with 3 to 6 ring atoms, or a monocyclic heterocyclic group having 5 or 6 ring atoms.

As used herein, the term "(C<sub>a</sub>-C<sub>b</sub>)alkyl" wherein a and b are integers refers to a straight or branched chain alkyl radical having from a to b carbon atoms. Thus when a is 1 and b is 6, for example, the term includes methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, t-butyl, n-pentyl and n-hexyl.

As used herein the term "divalent (C<sub>a</sub>-C<sub>b</sub>)alkylene radical" wherein a and b are integers means a saturated hydrocarbon chain having from a to b carbon atoms and two unsatisfied valences.

As used herein the unqualified term "cycloalkyl" refers to a saturated carbocyclic radical having from 3-8 carbon atoms and includes, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl.

As used herein the term "aryl" refers to a mono-, bi- or tri-cyclic carbocyclic aromatic radical, and to two such radicals covalently linked to each other, Illustrative of such radicals are phenyl, biphenyl and naphthyl.

As used herein the term "carbocyclic" refers to a cyclic radical whose ring atoms are all carbon and to two such cyclic radicals covalently linked to each other, and includes aryl, and cycloalkyl radicals.

As used herein the term "heteroaryl" refers to a mono-, bi- or tri-cyclic aromatic radical containing one or more heteroatoms selected from S, N and O. Illustrative of such radicals are thienyl, benzthienyl, furyl, benzfuryl, pyrrolyl, imidazolyl, benzimidazolyl, thiazolyl, benzthiazolyl, isothiazolyl, benzisothiazolyl, pyrazolyl, oxazolyl, benzoxazolyl, isoxazolyl, benzisoxazolyl, isothiazolyl, triazolyl, benztriazolyl, thiadiazolyl, oxadiazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, indolyl and indazolyl.

As used herein the unqualified term "heterocyclyl" or "heterocyclic" includes "heteroaryl" as defined above, and in particular means a mono-, bi- or tri-cyclic non-aromatic radical containing one or more heteroatoms selected from S, N and O, and to groups consisting of a monocyclic non-aromatic radical containing one or more such heteroatoms which is covalently linked to another such radical or to a monocyclic carbocyclic radical. Illustrative of such radicals are pyrrolyl, furanyl, thienyl, piperidinyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, thiadiazolyl, pyrazolyl, pyridinyl, pyrrolidinyl, pyrimidinyl, morpholinyl, piperazinyl, indolyl, morpholinyl, benzfuranyl, pyranal, isoxazolyl, benzimidazolyl, methylenedioxyphenyl, ethylenedioxyphenyl, maleimido and succinimido groups.

Unless otherwise specified in the context in which it occurs, the term "substituted" as applied to any moiety herein means substituted with at least one substituent selected from (C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>1</sub>-C<sub>6</sub>)alkoxy, hydroxy, hydroxy(C<sub>1</sub>-C<sub>6</sub>)alkyl, mercapto, mercapto(C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>1</sub>-C<sub>6</sub>)alkylthio, halo (including fluoro and chloro), trifluoromethyl, trifluoromethoxy, nitro, nitrile (-CN), oxo, phenyl, phenoxy, benzyl, benzyloxy, monocyclic carbocyclic or heterocyclic having from 5 to 7 ring atoms, -COOH, -COOR<sup>A</sup>, -COR<sup>A</sup>, -SO<sub>2</sub>R<sup>A</sup>, -CONH<sub>2</sub>, -SO<sub>2</sub>NH<sub>2</sub>, -CONHR<sup>A</sup>, -SO<sub>2</sub>NHR<sup>A</sup>, -CONR<sup>A</sup>R<sup>B</sup>, -SO<sub>2</sub>NR<sup>A</sup>R<sup>B</sup>, -NH<sub>2</sub>, -NHR<sup>A</sup>, -NR<sup>A</sup>R<sup>B</sup>, -OCONH<sub>2</sub>, -OCONHR<sup>A</sup>, -OCONR<sup>A</sup>R<sup>B</sup>, -NHCOR<sup>A</sup>,

$-\text{NHSO}_2\text{R}^{\text{A}}$ ,  $-\text{NHCOOR}^{\text{A}}$ ,  $-\text{NR}^{\text{B}}\text{COOR}^{\text{A}}$ ,  $-\text{NHSO}_2\text{OR}^{\text{A}}$ ,  $-\text{NR}^{\text{B}}\text{SO}_2\text{OR}^{\text{A}}$ ,  $-\text{NHCONH}_2$ ,  $-\text{NR}^{\text{A}}\text{CONH}_2$ ,  $-\text{NHCONHR}^{\text{B}}$ ,  $-\text{NR}^{\text{A}}\text{CONHR}^{\text{B}}$ ,  $-\text{NHCONR}^{\text{A}}\text{R}^{\text{B}}$ , or  $-\text{NR}^{\text{A}}\text{CONR}^{\text{A}}\text{R}^{\text{B}}$  wherein  $\text{R}^{\text{A}}$  and  $\text{R}^{\text{B}}$  are independently a ( $\text{C}_1\text{-C}_6$ )alkyl group.

The term "optional substituent" means one of the foregoing substituent groups.

As used herein the term "salt" includes base addition, acid addition and quaternary salts. Compounds of the invention which are acidic can form salts, including pharmaceutically or veterinarily acceptable salts, with bases such as alkali metal hydroxides, e.g. sodium and potassium hydroxides; alkaline earth metal hydroxides e.g. calcium, barium and magnesium hydroxides; with organic bases e.g. N-ethyl piperidine, dibenzylamine and the like. Those compounds (I) which are basic can form salts, including pharmaceutically or veterinarily acceptable salts with inorganic acids, e.g. with hydrohalic acids such as hydrochloric or hydrobromic acids, sulphuric acid, nitric acid or phosphoric acid and the like, and with organic acids e.g. with acetic, tartaric, succinic, fumaric, maleic, malic, salicylic, citric, methanesulphonic and p-toluene sulphonic acids and the like.

Some compounds of the invention contain one or more actual or potential chiral centres because of the presence of asymmetric carbon atoms. The presence of several asymmetric carbon atoms gives rise to a number of diastereoisomers with R or S stereochemistry at each chiral centre. The invention includes all such diastereoisomers and mixtures thereof.

#### The ring A

Examples of ring A include phenyl, naphthyl, 2-, 3- and 4-pyridyl, 5-pyrimidinyl, 2- and 3-thienyl, 2- and 3-furyl. Currently it is preferred that ring A is a phenyl ring.

Ring A may be optionally substituted by any of the substituents listed above in the definition of "optionally substituted". Examples of optional substituents on ring A or ring B include methyl, ethyl, methylenedioxy, ethylenedioxy, methoxy, ethoxy, methylthio, ethylthio, hydroxy, hydroxymethyl, hydroxyethyl,

mercapto, mercaptomethyl, mercaptoethyl, amino, mono- and di-methylamino, mono- and di-ethylamino, fluoro, chloro, bromo, cyano, N-morpholino, N-piperidinyl, N-piperazinyl (the latter being optionally C<sub>1</sub>-C<sub>6</sub> alkyl- or benzyl-substituted on the free ring nitrogen).

#### The radical $-(\text{Alk})_n-$

When present, the Alk radical acts as a spacer radical between the amino group on the pyrazolo[1,5-a]pyrimidine ring and the ring A, and may be, for example  $-\text{CH}_2-$ ,  $-\text{CH}_2\text{CH}_2-$ ,  $-\text{CH}_2\text{CH}(\text{CH}_3)-$ ,  $-\text{CH}_2\text{CH}_2\text{CH}_2-$ ,  $-\text{CH}=\text{CH}-$ ,  $-\text{CH}_2\text{CH}=\text{CH}-$ ,  $-\text{CH}_2\text{CH}=\text{CHCH}_2-$ ,  $-\text{CH}=\text{CHCH}=\text{CH}-$ ,  $-\text{C}\equiv\text{C}-$ ,  $-\text{CH}_2\text{C}\equiv\text{C}-$ , or  $-\text{CH}_2\text{C}\equiv\text{CCH}_2-$ . Presently it is preferred that Alk, when present be  $-\text{CH}_2-$  or  $-\text{CH}_2\text{CH}_2-$ .

However, in another preferred class of compounds with which the invention is concerned, n may be 0 so that the ring A is directly linked to the amino group on the pyrazolo[1,5-a]pyrimidine ring.

#### The Q Substituent of the Ring A

In the simplest structures with which the invention is concerned, each of p, r and s may be 0, and Z may be hydrogen, so that ring A is simply aryl or heteroaryl, optionally substituted as discussed above.

In other simple structures, p, r and s may again each be 0, and Z may be an optionally substituted carbocyclic or heterocyclic ring, for example phenyl, cyclopentyl, cyclohexyl, pyridyl, morpholino, piperidinyl, or piperazyl ring. In such cases, Q is a direct substituent in the optionally substituted ring A.

In more complex structures with which the invention is concerned, one or more of p, r and s may be 1, and Z may be hydrogen or an optionally substituted carbocyclic or heterocyclic ring. For example, p and/or s may be 1 and r may be 0, so that Z is linked to ring A by an alkylene radical, for example a C<sub>1</sub>-C<sub>3</sub> alkylene radical, which is optionally substituted. In other cases each of p, r, and s may be 1, in which cases, Z is linked to Ar<sup>1</sup> by an

alkylene radical which is interrupted by the hetero atom-containing X radical. In still other cases, p and s may be 0 and r may be 1, in which case Z is linked to Ar<sup>1</sup> via the hetero atom-containing X radical.

In one preferred embodiment, p is 0, r is 1, and X is a sulfonamide radical -NR<sup>A</sup>SO<sub>2</sub>- or a carboxamide radical -NR<sup>A</sup>C(=O)- (R<sup>A</sup> being as defined above, but preferably hydrogen), with the N atom linked to the ring A. In such cases s may be 1 and Z may be hydrogen, so that the group Q is an alkylsulfonamido or carboxamido substituent in the ring A; or s may be 0 and Q may be an optionally substituted carbocyclic or heterocyclic ring such as optionally substituted phenyl, eg 4-methylphenyl, so that the group Q is an optionally substituted phenylsulfonamido or carboxamido substituent in the ring A.

#### The substituent R<sub>1</sub>

R<sub>1</sub> represents a radical -(Alk<sup>3</sup>)<sub>a</sub>-(Y)<sub>b</sub>-(Alk<sup>4</sup>)<sub>d</sub>-B as defined above.

In one class of compounds of the invention a, b and d are all 0, and B is hydrogen or halo, so that the pyrimidine ring is either unsubstituted or substituted by halogen, for example chloro or bromo.

In another class of compounds of the invention, B is an optionally substituted monocyclic carbocyclic or heterocyclic ring, for example cyclopentyl, cyclohexyl, phenyl, 2-,3-, or 4-pyridyl, 2-, or 3-thienyl, 2-, or 3-furanyl, pyrrolyl, pyranyl, or piperidinyl ring. Optional substituents in ring B may be any of the substituents listed above in the definition of "optionally substituted". Examples of optional substituents on ring B include methyl, ethyl, methoxy, ethoxy, methylenedioxy, ethylenedioxy, methylthio, ethylthio, hydroxy, hydroxymethyl, hydroxyethyl, mercapto, mercaptomethyl, mercaptoethyl, amino, mono- and di-methylamino, mono- and di-ethylamino, fluoro, chloro, bromo, cyano, N-morpholino, N-piperidinyl, N-piperazinyl (the latter being optionally C<sub>1</sub>-C<sub>6</sub> alkyl- or benzyl-substituted on the free ring nitrogen). In such cases, ring B is linked to the pyrimidine ring via linker radical of various types depending on the values of a, b and d, and the identities of Alk<sup>3</sup>, Y and Alk<sup>4</sup>. For example, when b is 0, the ring B is linked to the pyrimidine ring via an optionally substituted

C<sub>1</sub>-C<sub>6</sub> alkylene radical; and when a and d are 0 and b is 1 the ring B is linked to the pyrimidine ring via an oxygen or sulfur link or via an amino link -NR<sup>A</sup>- wherein R<sup>A</sup> is hydrogen or C<sub>1</sub>-C<sub>6</sub> alkyl such as methyl or ethyl.

In another class of compounds of the invention b is 0, at least one of a and d is 1, and B is hydrogen, so that the pyrimidine ring is substituted by a C<sub>1</sub>-C<sub>6</sub> alkyl group, for example methyl, ethyl, and n- or iso-propyl, which may itself be substituted by substituents listed above in the definition of "optionally substituted. Examples of optional substituents include methoxy, ethoxy, methylthio, ethylthio, hydroxy, hydroxymethyl, hydroxyethyl, mercapto, mercaptomethyl, mercaptoethyl, amino, mono- and di-methylamino, mono- and di-ethylamino, fluoro, chloro, bromo, and cyano.

In a further class of compounds of the invention a is 1 or 0, b is 1, Y is -NR<sup>A</sup>-, and the radical -(Alk<sup>4</sup>)<sub>d</sub>-B taken together with R<sub>A</sub> and the nitrogen to which they are attached form an optionally substituted heterocyclic ring such as a ring piperidinyl, morpholinyl or piperazinyl ring, optionally substituted, for example, by hydroxy, mercapto, methoxy, ethoxy, methylthio, ethylthio, amino, mono- or dimethyl amino, mono- or diethyl amino, nitro, or cyano. In the case of a piperazinyl ring, the second ring nitrogen may optionally be substituted by, for example methyl or ethyl.

Specific examples of R<sub>1</sub> include hydrogen; chloro; phenyl; phenyl substituted by chloro, bromo, hydroxy, methyl; 2- or 3 thienyl; 3, 5-dimethylisoxazolyl; cyclohexyloxy; and cyclopentyloxy;

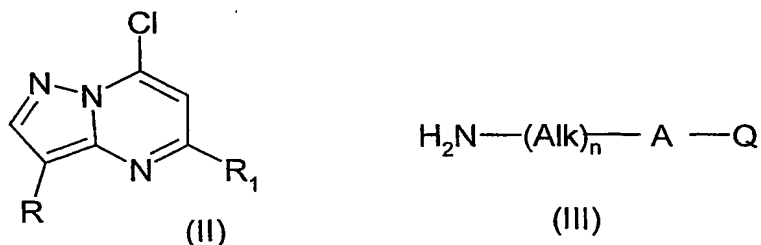
#### The group R

R may be, for example, hydrogen, bromo methyl, ethyl, n-propyl, iso-propyl, n-, sec- or tert-butyl, phenyl, benzyl, cyclopropyl, cyclopentyl, cyclohexyl, 2-, 3-, or 4- pyridyl, phenyl, pyridyl, morpholino, piperidinyl, or piperazyl ring At present it is preferred that R be isopropyl.

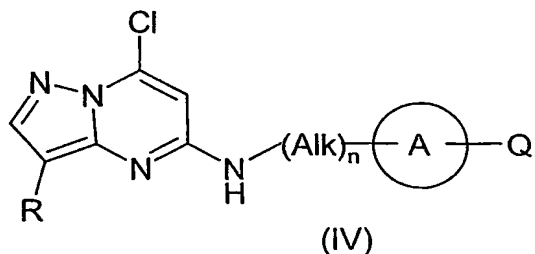
Specific compounds with which the invention is concerned include those identified in the Examples.

Compounds with which the invention is concerned may be prepared by literature methods, such as those of the preparative Examples herein, and methods analogous thereto.

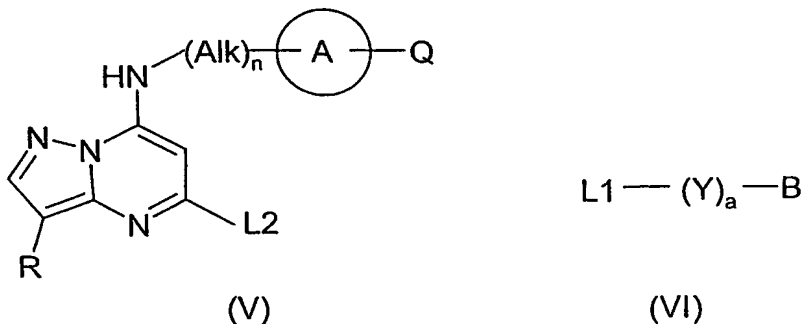
For example, compounds of the invention wherein  $R_1$  is hydrogen or halo may be prepared by reacting the chloro or dichloro compound (II) with the amine (III),



and in the case where  $R_1$  is halo, separating the desired compound (I) from any resultant contaminant regioisomer (IV):

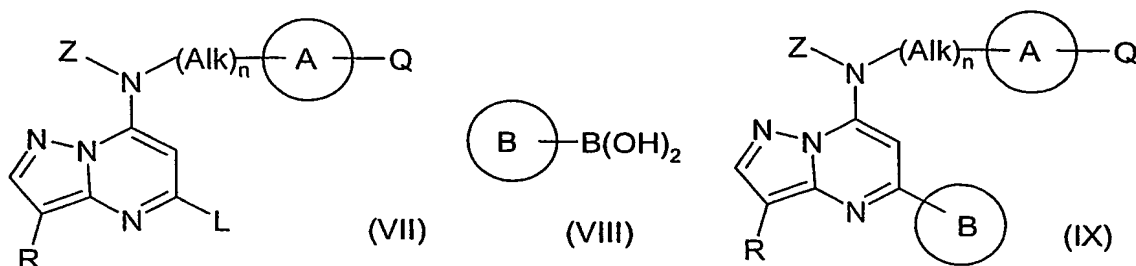


To prepared compounds of the invention wherein  $R_1$  is a radical  $-(Y)_a-B$  the general synthetic procedure is based on the coupling of compounds (V) and (VI)

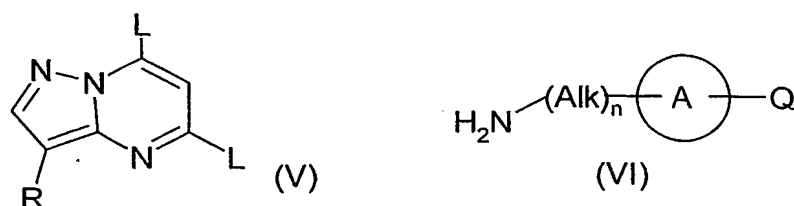


wherein L1 and L2 represent components of a leaving group L1L2.

Thus, to prepare compounds (I) wherein  $R_1$  is  $-(Y)_a-B$  wherein  $a=0$  and B is an aryl or heteroaryl ring, a compound of formula (VII) wherein Z is an N-protecting group may be reacted with the corresponding aryl or heteroaryl borohydrate compound (VIII) to prepare an intermediate compound (IX), from which the N-protecting group Z may be removed to prepare the desired compound (I).



The starting compound (II) may be prepared by reaction of a compound (V) with an amine (VI):



In the above formulae (II) – (VI), L signifies a leaving group such as halo, for example chloro. Ring A, Alk, Q and n are as defined in relation to formula (I).

Likewise, to prepare compounds (I) wherein  $R_1$  is  $-(Y)_a-B$  wherein  $a=1$ , and Y is  $-O-$  the compound (VII), where L is chloro, for example, may be reacted with the hydroxy compound HY-B.

The compounds of the invention are inhibitors of CDK2 and are thus useful in the treatment of diseases which are mediated by excessive or inappropriate CDK2 activity such as cancers, leukemias and other disease states associated with uncontrolled cell proliferation such as psoriasis and restenosis

Accordingly, the invention also provides:

(i) a method of treatment of diseases or conditions mediated by excessive or inappropriate CDK2 activity in mammals, particularly humans, which method comprises administering to the mammal an amount of a compound of formula (I) as defined above, or a salt, hydrate or solvate thereof, effective to inhibit said CDK2 activity.; and

(ii) a compound of formula (I) as defined above, or a salt hydrate or solvate thereof, for use in human or veterinary medicine, particularly in the treatment of diseases or conditions mediated by excessive or inappropriate CDK2 activity;

It will be understood that the specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, rate of excretion, drug combination and the causative mechanism and severity of the particular disease undergoing therapy. In general, a suitable dose for orally administrable formulations will usually be in the range of 0.1 to 3000 mg once, twice or three times per day, or the equivalent daily amount administered by infusion or other routes. However, optimum dose levels and frequency of dosing will be determined by clinical trials as is conventional in the art.

The compounds with which the invention is concerned may be prepared for administration by any route consistent with their pharmacokinetic properties. The orally administrable compositions may be in the form of tablets, capsules, powders, granules, lozenges, liquid or gel preparations, such as oral, topical, or sterile parenteral solutions or suspensions. Tablets and capsules for oral administration may be in unit dose presentation form, and may contain conventional excipients such as binding agents, for example syrup, acacia, gelatin, sorbitol, tragacanth, or polyvinyl-pyrrolidone; fillers for example lactose, sugar, maize-starch, calcium phosphate, sorbitol or glycine; tableting lubricant, for example magnesium stearate, talc, polyethylene glycol or silica; disintegrants for example potato starch, or acceptable wetting agents such as

sodium lauryl sulphate. The tablets may be coated according to methods well known in normal pharmaceutical practice. Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example sorbitol, syrup, methyl cellulose, glucose syrup, gelatin hydrogenated edible fats; emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; non-aqueous vehicles (which may include edible oils), for example almond oil, fractionated coconut oil, oily esters such as glycerine, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl p-hydroxybenzoate or sorbic acid, and if desired conventional flavouring or colouring agents.

For topical application to the skin, the drug may be made up into a cream, lotion or ointment. Cream or ointment formulations which may be used for the drug are conventional formulations well known in the art, for example as described in standard textbooks of pharmaceuticals such as the British Pharmacopoeia.

The active ingredient may also be administered parenterally in a sterile medium. Depending on the vehicle and concentration used, the drug can either be suspended or dissolved in the vehicle. Advantageously, adjuvants such as a local anaesthetic, preservative and buffering agents can be dissolved in the vehicle.

The following non-limiting Examples illustrate the invention:

In the Examples, reactions that are specified as being carried out in a microwave oven were conducted in a Smith Synthesizer. Proton NMR experiments were conducted on a Bruker DPX400 ultra shield NMR spectrometer in the solvent specified.

# Open Access LC-MS: Method A

HPLC: HP1100  
 Column: Luna 3 $\mu$ m, C18(2), 30mm x 4.6mm i.d. from Phenomenex  
 Temperature: 22°C  
 Solvents: A - Water + 10mmol ammonium acetate + 0.08% (v/v) formic acid  
               B – 95% Acetonitrile / 5% Solvent A + 0.08% (v/v) formic acid  
 Flow rate: 2ml/min

Time (mins)	% Solvent A	% Solvent B	Flow (ml/min)
0	95	5	2
0.25	95	5	2
2.50	5	95	2
2.55	5	95	3
3.60	5	95	3
3.65	5	95	3
3.70	5	95	2
3.75	95	5	2

## Gradient

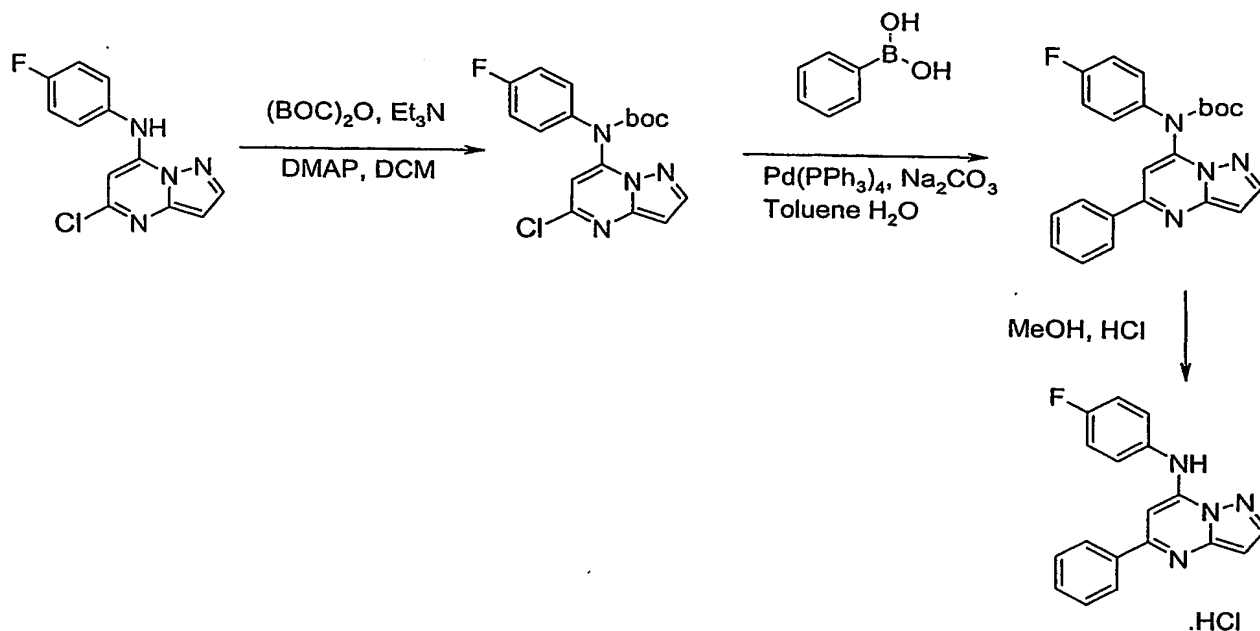
Total acquisition time is 3.75minutes

Detection: UV detection at 230nm, 254nm and 270nm

Mass Spec: HP1100 MSD, Series A

Ionisation is positive or negative ion electrospray

Molecular weight scan range is 120-1000

**Example 1****Step 1****5-Chloro-7-(4-fluorophenylamino)pyrazolo[1,5-a]pyrimidine**

To a solution of 5,7-dichloropyrazolo[1,5-a]pyrimidine<sup>1</sup> (0.35 g, 1.86 mmol) in ethanol ( $15 \text{ cm}^3$ ) was added 4-fluoroaniline ( $0.35 \text{ cm}^3$ , 3.72 mmol). The reaction mixture was heated under reflux for 1 hour. The reaction mixture was concentrated *in vacuo* and the product purified on silica eluting with 15% ethyl acetate in hexanes, to yield the title compound as a white solid (0.42 g, 86%).

$\delta_{\text{H}}$  (400 MHz;  $\text{d}_4$ -MeOH) 8.02 (1 H, d,  $J$  2.2 Hz), 7.40-7.36 (2 H, m), 7.21 (2H, t,  $J$  6.7), 6.32 (1 H, d,  $J$  2.2 Hz), 5.97 (1H, s).

$m/z$  263 and 265 (each  $M+H$ , 100% and 30%) retention time 2.54 min (Method A).

**Step 2****5-Chloro-7-(N-tert-butoxycarbonyl-4-fluorophenylamino)pyrazolo[1,5-a]pyrimidine**

To a solution of 5-chloro-7-(4-fluorophenylamino)pyrazolo[1,5-a]pyrimidine (0.15 g, 0.57 mmol) in dichloromethane (10 cm<sup>3</sup>) was added di-*tert*-butyl dicarbonate (0.37 g, 1.71 mmol), triethylamine (0.096 cm<sup>3</sup>, 0.69 mmol) and 4-dimethylaminopyridine (0.01 g, 0.082 mmol). The reaction mixture was stirred at room temperature for 16 h. The reaction was diluted with water (30 cm<sup>3</sup>) and extracted with dichloromethane (3 × 20 cm<sup>3</sup>). The combined organic fractions were washed with brine then dried with magnesium sulphate and concentrated *in vacuo*. The product was purified on silica eluting with 20% ethyl acetate in hexanes, to yield the title compound as a white solid (0.191 g, 92%).

$\delta_{\text{H}}$  (400 MHz; d-CHCl<sub>3</sub>) 8.09 (1 H, d, *J* 2.3 Hz), 7.29-7.25 (2 H, m), 6.99 (2H, t, *J* 8.1), 6.63 (1 H, d, *J* 2.3 Hz), 6.60 (1H, s), 1.30 (9H, s).

### Step 3

#### 5-Phenyl-7-(*N*-tert-butoxycarbonyl-4-fluorophenylamino)pyrazolo[1,5-a]pyrimidine

To a solution of 5-chloro-7-(*N*-tert-butoxycarbonyl-4-fluorophenylamino)pyrazolo[1,5-a]pyrimidine (0.05 g, 0.14 mmol) in toluene (3.5 cm<sup>3</sup>) and water (1 cm<sup>3</sup>) was added phenyl boronic acid (0.02 g, 0.16 mmol) and sodium carbonate (0.031 g, 0.29 mmol). The solution was degassed by bubbling nitrogen through the reaction mixture for 5 min. Tetrakis(triphenylphosphine)palladium(0) (0.015 g, 0.012 mmol) was added to the mixture and the reaction was heated at reflux for 16 h. The reaction mixture was concentrated *in vacuo* and purified on silica eluting with 20% ethyl acetate in hexanes to yield the title compound as an off-white solid (0.048 g, 86%).

$\delta_{\text{H}}$  (400 MHz; d-CHCl<sub>3</sub>) 8.11 (1 H, d, *J* 2.3 Hz), 7.99-7.97 (2 H, m), 7.44-7.42 (3H, m), 7.34-7.31 (2 H, m), 7.08 (1H, s), 6.97 (2H, t, *J* 8.3 Hz), 6.73 (1H, d, *J* 2.3 Hz), 1.31 (9H, s).

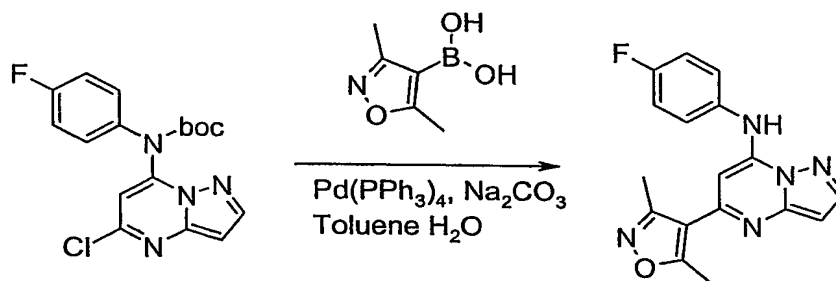
*m/z* 405 (*M*+H, 80%), 349 (*M*+H-56, 70%), 305 (*M*+H-100, 100%), retention time 2.92 min (Method A).

**Step 4****5-Phenyl-7-(4-fluorophenylamino)pyrazolo[1,5-a]pyrimidine hydrochloride**

To a solution of 5-phenyl-7-(*N*-tert-butoxycarbonyl-4-fluorophenylamino)pyrazolo[1,5-a]pyrimidine (0.045 g, 0.11 mmol) in methanol (1 cm<sup>3</sup>) was added a solution of hydrochloric acid (3 M in methanol, 10 cm<sup>3</sup>). The reaction mixture was stirred at room temperature for 3 h then concentrated *in vacuo*. The product was purified by crystallisation from ethyl acetate, to yield the title compound as a white solid (0.016 g, 42%).

$\delta_{\text{H}}$  (400 MHz; d<sub>4</sub>-MeOH) 8.25 (1 H, d, *J* 2.2 Hz), 7.74-7.72 (2 H, m), 7.59-7.51 (5H, m), 7.27 (2H, t, *J* 8.6 Hz), 6.60 (1H, d, *J* 2.2 Hz), 6.39 (1H, s).

*m/z* 305 (*M*+H, 100%), retention time 2.68 min (Method A).

**Example 2****5-(3,5-Dimethylisoxazole)-7-(4-fluorophenylamino)pyrazolo[1,5-a]pyrimidine**

To a solution of 5-chloro-7-(*N*-tert-butoxycarbonyl-4-fluorophenylamino)pyrazolo[1,5-a]pyrimidine (Example 1, Step 2) (0.05 g, 0.14 mmol) in 1,4-dioxane (3.5 cm<sup>3</sup>) and water (1 cm<sup>3</sup>) was added 3,5-dimethylisoxazole-4-boronic acid (0.023 g, 0.16 mmol) and sodium carbonate (0.031 g, 0.29 mmol). The solution was degassed by bubbling nitrogen through the mixture for 5 min. Tetrakis(triphenylphosphine)palladium(0) (0.015 g, 0.012 mmol) was added to the mixture and the reaction heated at 150°C for

10 min in a microwave oven. The reaction mixture was concentrated *in vacuo* and purified on silica eluting with 2% methanol in dichloromethane to yield the title compound as a white solid (0.021 g, 47%).

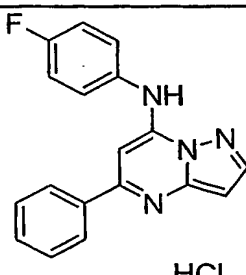
$\delta_{\text{H}}$  (400 MHz;  $\text{d-CHCl}_3$ ) 8.03 (1 H, d,  $J$  2.3 Hz), 7.97 (1 H, s), 7.33-7.30 (2H, m), 7.13 (2H, t,  $J$  8.5 Hz), 6.52 (1H, d,  $J$  2.3 Hz), 6.13 (1H, s), 2.50 (3H, s), 2.34 (3H, s).

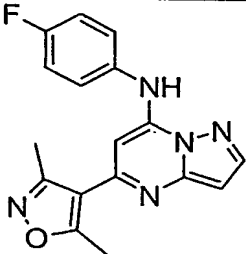
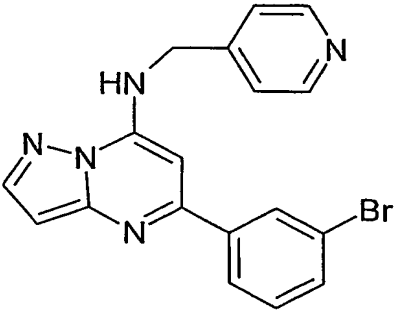
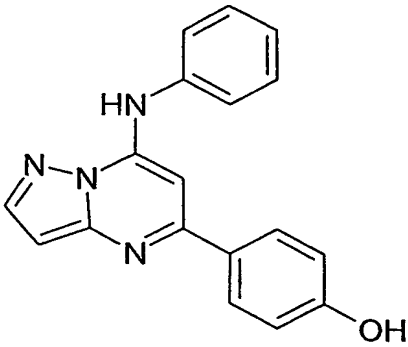
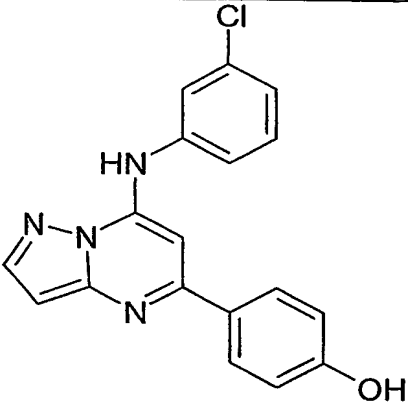
$m/z$  324 ( $M+H$ , 100%), retention time 2.51 min (Method A).

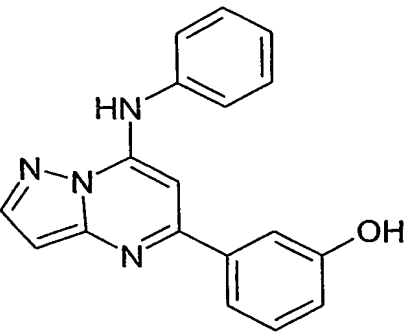
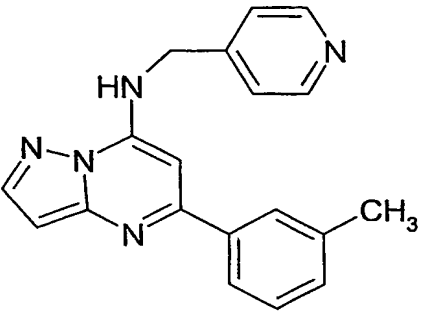
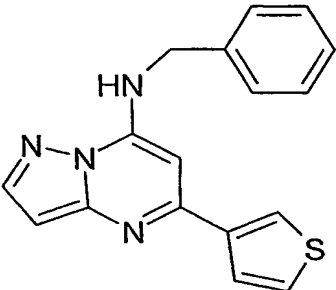
1. T. Novinson et al., Journal of Medicinal Chemistry (1976), 19(4), 512-16.

### Examples 3 - 8

The compounds of Examples 3 – 8, listed in the following Table 1 were commercially available from BioFocus (BioFocus plc, Chesterford Park, Saffron Walden, Essex, CB10 1XL). The compounds of Examples 1 and 2 are also included in the Table. All compounds were tested for CDK2 inhibitory activity in the assay described below in the Assay section. The result obtained in each case is given in the Table.

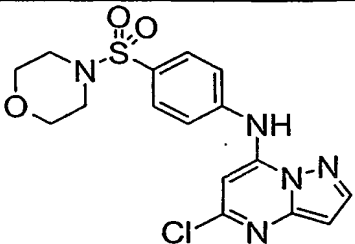
Structure	Example No	CDK-2/cyclin A IC <sub>50</sub> (uM)
 .HCl	1	5.5

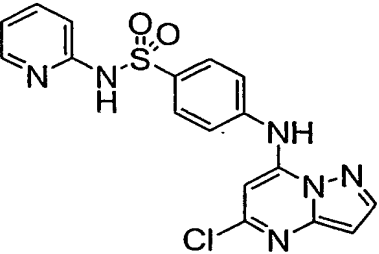
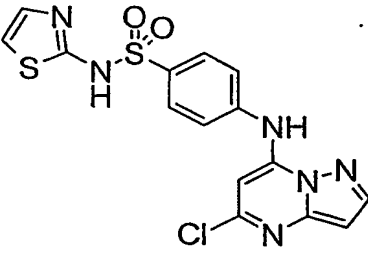
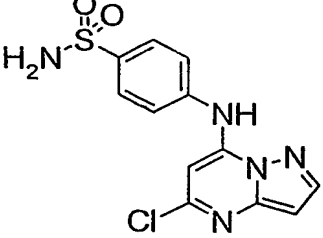
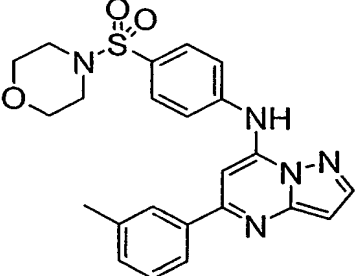
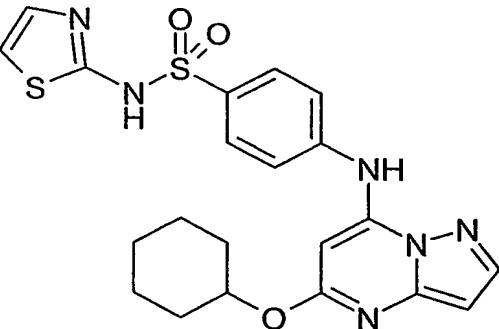
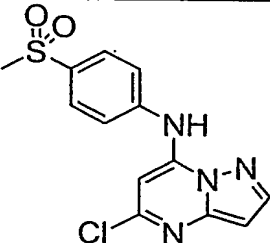
	2	13
	3	2.0
	4	3.8
	5	4.0

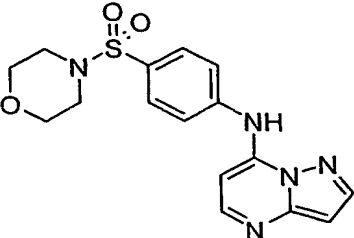
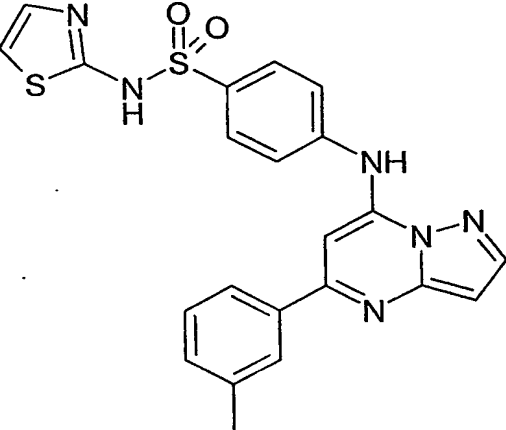
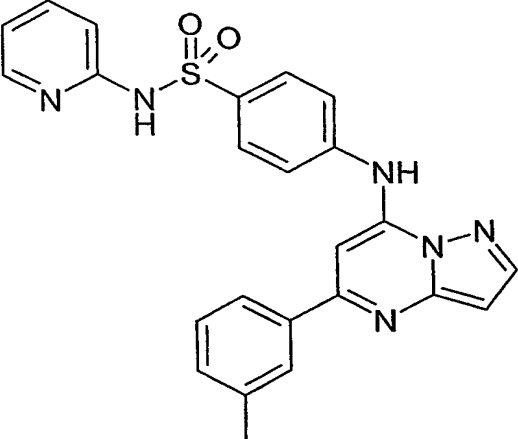
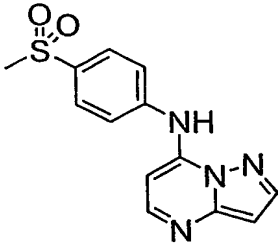
	6	5.7
	7	7.2
	8	7.6

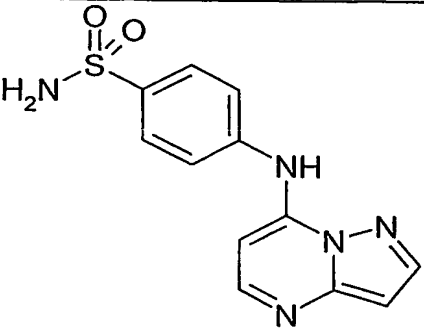
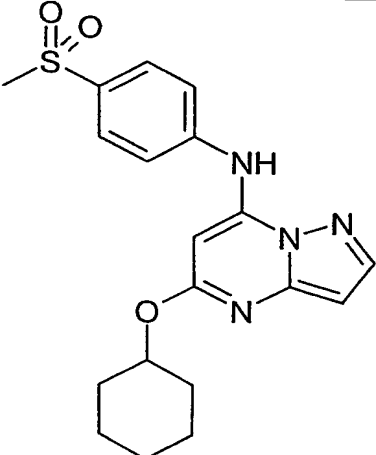
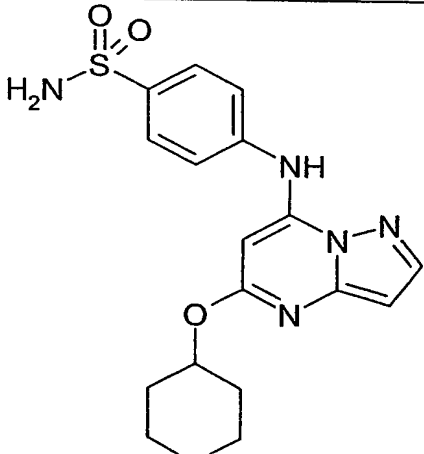
The compounds of Examples 9 – 23, listed in the following Table 2 were prepared by methods analogous to those of Example 1, All compounds were tested for CDK2 inhibitory activity in the assay described below in the Assay section. The result obtained in each case is given in the Table.

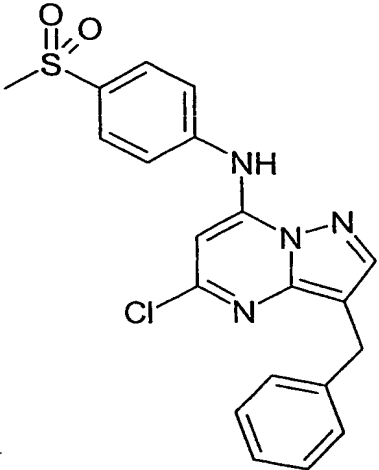
Table 2

Structure	Example	CDK2 IC <sub>50</sub> ( $\mu$ M)
	9	0.99

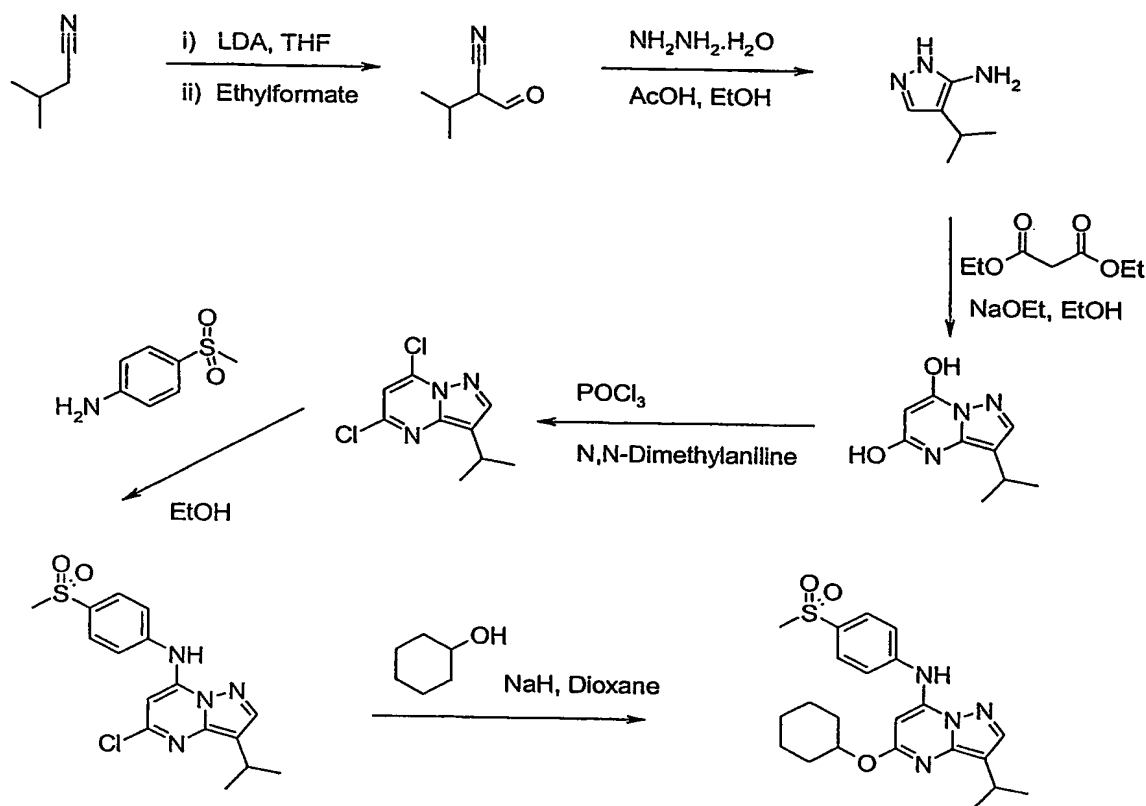
	10	1.63
	11	1.31
	12	0.72
	13	1.76
	14	0.59
	15	1.99

	16	3.35
	17	3.20
	18	0.95
	19	10.40

	20	1.8
	21	1.3
	22	0.30

 <chem>Cs(=O)(=O)c1ccc(Nc2nc3cc(Cl)nc3c2Cc4ccccc4)cc1</chem>	23	>200
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## Examples 24 and 25



## Step 1: 2-formyl-3-methylbutanenitrile

To a solution of diisopropyl amine ( $25.2 \text{ cm}^3$ ,  $0.180 \text{ mol}$ ) in tetrahydrofuran ( $100 \text{ cm}^3$ ) at  $-78^\circ\text{C}$  was added dropwise  $n$ -butyllithium ( $1.6 \text{ M}$  in hexanes,  $112.8 \text{ cm}^3$ ,  $0.180 \text{ mol}$ ). The reaction was stirred at  $-78^\circ\text{C}$  for 30 min. Isovaleronitrile ( $18.9 \text{ cm}^3$ ,  $0.180 \text{ mol}$ ) was added and the reaction stirred for 10 min. The reaction mixture was added to a solution of ethyl formate ( $15.3 \text{ cm}^3$ ,  $0.190 \text{ mol}$ ) in tetrahydrofuran ( $50 \text{ cm}^3$ ) at  $-78^\circ\text{C}$ . The reaction was stirred at  $-78^\circ\text{C}$  for 30 min. then allowed to warm to room temperature and stirred for 16 h. The reaction was diluted with aqueous hydrochloric acid ( $300 \text{ cm}^3$ ,  $1\text{M}$ ) until the pH was approximately  $\text{pH} = 3$ . The product was extracted with ethyl acetate ( $3 \times 100 \text{ cm}^3$ ). The combined organic fractions were washed with brine then dried over magnesium sulphate and concentrated *in vacuo*. The

product was purified on silica gel eluting with 50% diethyl ether in hexanes, to yield the title compound as a yellow oil (14.6 g, 73%).

$\delta_H$  (400 MHz;  $d\text{-CHCl}_3$ ) 9.51 (1 H, d,  $J$  1.1 Hz), 3.35 (1H, dd,  $J$  4.9, 1.0), 2.43-2.38 (1H, m), 1.12 (3H, d,  $J$  6.6), 1.05 (3H, d,  $J$  6.7).

### Step 2: 3-amino-4-isopropylpyrazole

To a solution of 2-formyl-3-methyl-butanenitrile (9.47 g, 85.2 mmol) in ethanol (250  $\text{cm}^3$ ) was added hydrazine hydrate (6.27  $\text{cm}^3$ , 110.8 mmol) and acetic acid (8.30  $\text{cm}^3$ , 144.8 mmol). The reaction was heated under reflux for 16 h. The reaction was concentrated *in vacuo* to approximately one third the original volume. The residue was diluted with aqueous sodium bicarbonate (100  $\text{cm}^3$ , saturated solution) and the product extracted with dichloromethane (3  $\times$  100  $\text{cm}^3$ ). The combined organic fractions were washed with brine then dried over magnesium sulphate and concentrated *in vacuo* to yield the crude product as a brown solid (9.35 g, 88%).

$\delta_H$  (400 MHz;  $d\text{-CHCl}_3$ ) 6.99 (1 H, s), 2.55 (1H, sept,  $J$  6.8), 1.06 (6H, d,  $J$  6.8).

$m/z$  126 ( $M+H$ , 100%), retention time 1.21 min (Method A).

### Step 3: 3-isopropyl-5,7-dihydroxypyrazolo[1,5-a]pyrimidine

Sodium (0.98 g, 42.8 mmol) was dissolved in ethanol (200  $\text{cm}^3$ ) and to the solution was added 3-amino-4-isopropyl-pyrazole (4.46 g, 35.6 mmol) and diethyl malonate (5.95  $\text{cm}^3$ , 39.2 mmol). The reaction was heated under reflux for 16 h. The reaction was concentrated *in vacuo* and the residue dissolved in water (50  $\text{cm}^3$ ). The reaction was acidified to approx pH = 3 with hydrochloric acid (2N) and the precipitate formed was collected by filtration. The solid was washed with water (3  $\times$  50  $\text{cm}^3$ ) and dried *in vacuo* to yield the product as an off-white solid (3.95 g, 57%).

$\delta_H$  (400 MHz;  $d_6\text{-DMSO}$ ) 7.94 (1 H, s), 7.84 (1H, s), 5.06 (1H, s), 3.91 (2H, s), 3.23-3.08 (2H, m), 1.32 (6H, d,  $J$  6.8), 1.30 (6H, d,  $J$  6.8).

$m/z$  194 ( $M+H$ , 100%), retention time 1.38 min (Method A).

#### Step 4: 3-isopropyl-5,7-dichloropyrazolo[1,5-a]pyrimidine

3-isopropyl-5,7-dihydroxypyrazolo[1,5-a]pyrimidine (3.95 g, 20.4 mmol) and *N,N*-dimethylaniline (1.73 cm<sup>3</sup>, 13.6 mmol) were suspended in phosphorous oxychloride (38.1 cm<sup>3</sup>, 0.41 mol). The reaction was heated under reflux for 16 h, over which time the 3-isopropyl-5,7-dihydroxypyrazolo[1,5-a]pyrimidine dissolved. The reaction was concentrated *in vacuo* and the residue poured onto ice (approx 50 g). The product was extracted with dichloromethane (3 × 50 cm<sup>3</sup>). The combined organic fractions were washed with brine then dried over magnesium sulphate and concentrated *in vacuo*. The product was purified on silica eluting with 5% ethyl acetate in hexanes, to yield the title compound as a yellow solid (3.90 g, 83%).

$\delta_H$  (400 MHz; *d*-CHCl<sub>3</sub>) 7.92 (1 H, s), 6.74 (1H, s), 3.14 (1H, sept, *J* 6.9), 1.19 (6H, d, *J* 6.9).

$m/z$  230 and 232 each ( $M+H$ , 100% and 65%), retention time 2.65 min (Method A).

#### Step 5: 3-isopropyl-5-chloro-7-(4-methylsulphonylaminophenyl)pyrazolo[1,5-a]pyrimidine (Example 24)

To a solution of 3-isopropyl-5,7-dichloropyrazolo[1,5-a]pyrimidine (0.50 g, 2.17 mmol) in ethanol (20 cm<sup>3</sup>) was added 4-methylsulphonylaniline (0.50 g, 2.39 mmol). The reaction was heated under reflux for 16 h. The reaction was concentrated *in vacuo* and the residue triturated with hot methanol (2 × 10 cm<sup>3</sup>) to yield the product as a white solid (0.56 g, 70%).

$\delta_H$  (400 MHz; *d*<sub>6</sub>-DMSO) 10.53 (1H, s), 8.05 (1 H, s), 7.85 (2H, d, *J* 6.8), 7.60 (2H, d, *J* 6.8), 6.28 (1H, s), 3.11 (3H, s), 3.02 (1H, sept, *J* 6.9), 1.18 (6H, d, *J* 6.9).

*m/z* 365 and 367 each (*M*+*H*, 100% and 35%), retention time 2.57 min (Method A).

**Step 6: 3-isopropyl-5-cyclohexanyloxy-7-(4-methylsulphonylaminophenyl)pyrazolo[1,5-a]pyrimidine (Example 25)**

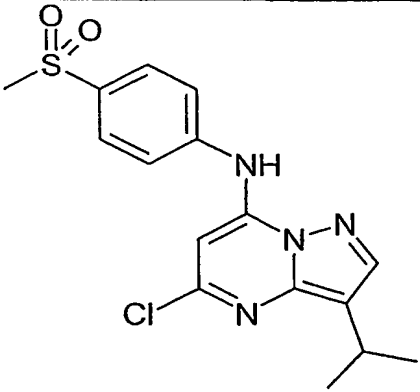
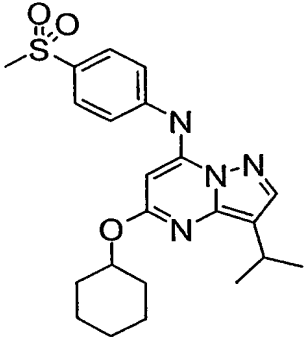
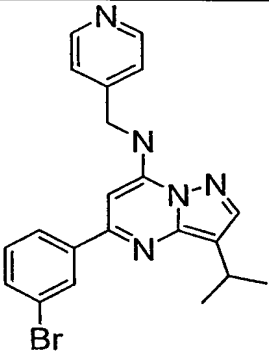
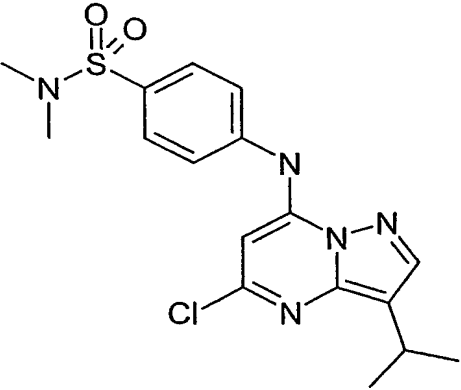
To a solution of cyclohexanol (0.14 cm<sup>3</sup>, 1.37 mmol) in dioxane (5 cm<sup>3</sup>) was added sodium hydride (0.11 g, 60% by wt in oil, 2.74 mmol). Once effervescence had ceased 3-isopropyl-5-chloro-7-(4-methylsulphonylaminophenyl)pyrazolo[1,5-a]pyrimidine (0.10 g, 0.27 mmol) was added. The reaction was heated via a microwave reactor, in a sealed tube, at 120 °C for 20 min. The reaction was poured into water (20 cm<sup>3</sup>) and the product extracted with ethyl acetate (3 × 20 cm<sup>3</sup>). The combined organic fractions were dried with brine then magnesium sulphate and concentrated *in vacuo*. The product was purified on silica eluting with 25-50% ethyl acetate in hexanes, to yield the title compound as a white solid (0.008 g, 7%).

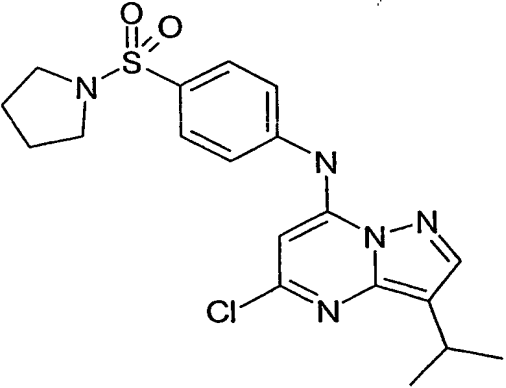
$\delta_{\text{H}}$  (400 MHz; d-CDCl<sub>3</sub>) 8.18 (1 H, s), 7.98 (2H, d, *J* 6.8), 7.78 (1H, s), 7.48 (2H, d, *J* 6.8), 5.17-5.13 (1H, m), 3.15 (1H, sept, *J* 6.8), 3.07 (3H, s), 2.04-2.02 (2H, m), 1.80-1.77 (2H, m), 1.60-1.43 (6H, m), 1.35 (6H, d, *J* 6.9).

*m/z* 429 (*M*+*H*, 100%), retention time 3.05 min (Method A).

The compounds of Examples 26 – 28, listed in the following Table 3 were prepared by methods analogous to those of Examples 24 and 25. The compounds of Examples 24 and 25 are also included in the Table. All compounds were tested for CDK2 inhibitory activity in the assay described below in the Assay section. The result obtained in each case is given in the Table.

Table 3

Structure	Example	CDK2 IC <sub>50</sub> ( $\mu$ M)
	24	0.22
	25	0.95
	26	0.53
	27	0.24

	28	0.27
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#### Assay Conditions:

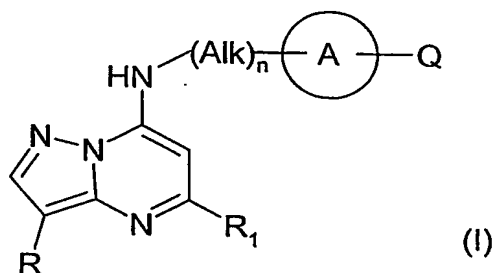
Assays for the cyclin dependent kinase activity were carried out by monitoring the phosphorylation of a synthetic peptide, HATTPKKRK. The assay mixture containing the inhibitor and CDK-2 enzyme, complexed with cyclin A (0.4U/ml) was mixed together in a microtiter plate in a final volume of 50 $\mu$ l and incubated for 40 min at 30°C. The assay mixture contained 0.1 mM unlabeled ATP, 0.01 $\mu$ Ci/ $\mu$ l  $^{33}$ P- $\gamma$ -ATP, 0.03mM peptide, 0.1mg/ml BSA, 7.5mM magnesium acetate, 50mM HEPES-NaOH, pH 7.5. The reaction was stopped by adding 50 $\mu$ l of 50mM phosphoric acid. 90 $\mu$ l of the mixture were transferred to a pre-wetted 96-well Multiscreen MAPHNOB filtration plate (Millipore) and filtered on a vacuum manifold. The filter plate was washed with 3 successive additions of 200 $\mu$ l 50mM phosphoric acid and then with 100 $\mu$ l methanol. The filtration plate was dried for 10 min at 65°C, scintillant added and phosphorylated peptide quantified in a scintillation counter (Trilux, PerkinElmer)

HEPES is N-[2-Hydroxyethyl]piperazine-N'-[2-ethanesulfonic acid]

BSA is bovine serum albumin.

# Claims.

1. The use of a compound of formula (I) or a salt, N-oxide, hydrate or solvate thereof, in the preparation of a composition for inhibition of CDK2 activity:



wherein

Ring A is optionally substituted aryl or heteroaryl,

Alk represents an optionally substituted divalent C<sub>1</sub>-C<sub>6</sub> alkylene radical;

n is 0 or 1;

Q represents a radical of formula  $-(\text{Alk}^1)_p-(\text{X})_r-(\text{Alk}^2)_s-\text{Z}$  wherein in any compatible combination

Z is hydrogen or an optionally substituted carbocyclic or heterocyclic ring,

Alk<sup>1</sup> and Alk<sup>2</sup> are optionally substituted divalent C<sub>1</sub>-C<sub>6</sub> alkylene radicals,

X represents -O-, -S-, -(C=O)-, -(C=S)-, -SO<sub>2</sub>-, -SO-, -C(=O)O-, -OC(=O)-, -C(=O)NR<sup>A</sup>-, -NR<sup>A</sup>C(=O)-, -C(=S)NR<sup>A</sup>-, -NR<sup>A</sup>C(=S)-, -SO<sub>2</sub>NR<sup>A</sup>-, -NR<sup>A</sup>SO<sub>2</sub>-, -OC(=O)NR<sup>A</sup>-, -NR<sup>A</sup>C(=O)O-, or -NR<sup>A</sup>- wherein R<sup>A</sup> is hydrogen or C<sub>1</sub>-C<sub>6</sub> alkyl, and

p, r and s are independently 0 or 1,

$R_1$  represents a radical  $-(Alk^3)_a-(Y)_b-(Alk^4)_d-B$  wherein a, b and d are independently 0 or 1,

$Alk^3$  and  $Alk^4$  are optionally substituted divalent  $C_1-C_3$  alkylene radicals,

Y represents  $-O-$ ,  $-S-$ , or  $-NR^A-$  wherein  $R^A$  is hydrogen or  $C_1-C_6$  alkyl,

B represents hydrogen or halo, or an optionally substituted monocyclic carbocyclic or heterocyclic ring with 5 or 6 ring members, or in the case where Y is  $-NR^A-$  and b is 1, then  $R^A$  and the radical  $-(Alk^4)_d-B$  taken together with the nitrogen to which they are attached may form an optionally substituted heterocyclic ring,

R represents hydrogen, bromo,  $C_1-C_6$  alkyl, phenyl, benzyl, cycloalkyl with 3 to 6 ring atoms, or a monocyclic heterocyclic group having 5 or 6 ring atoms.

2. The use as claimed in claim 1 wherein ring A is phenyl, naphthyl, 2-,3- or 4-pyridyl, 5-pyrimidinyl, 2- or 3-thienyl, 2- or 3-furyl.
3. The use as claimed in claim 1 wherein ring A is phenyl.
4. The use as claimed in any of claims 1 to 3 wherein ring A is substituted by methyl, ethyl, methylenedioxy, ethylenedioxy, methoxy, ethoxy, methylthio, ethylthio, hydroxy, hydroxymethyl, hydroxyethyl, mercapto, mercaptomethyl, mercaptoethyl, amino, mono- or di-methylamino, mono- or di-ethylamino, fluoro, chloro, bromo, cyano, N-morpholino, N-piperidinyl, or N-piperazinyl, the latter being optionally  $C_1-C_6$  alkyl- or benzyl-substituted on the free ring nitrogen.
5. The use as claimed in any of the preceding claims wherein  $R_1$  is hydrogen, chloro or bromo.

6. The use as claimed in any of claims 1 to 5 wherein in the radical  $R_1$ , B is an optionally substituted cyclopentyl, cyclohexyl, phenyl, 2-,3-, or 4-pyridyl, 2-, or 3-thienyl, 2-, or 3-furanyl, pyrrolyl, pyranyl, or piperidinyl ring.
7. The use as claimed in claim 5 wherein the ring B is substituted by methyl, ethyl, methoxy, ethoxy, methylenedioxy, ethylenedioxy, methylthio, ethylthio, hydroxy, hydroxymethyl, hydroxyethyl, mercapto, mercaptomethyl, mercaptoethyl, amino, mono- and di-methylamino, mono- and di-ethylamino, fluoro, chloro, bromo, cyano, N-morpholino, N-piperidinyl, or N-piperazinyl, the latter being optionally  $C_1$ - $C_6$  alkyl- or benzyl-substituted on the free ring nitrogen.
8. The use as claimed in claim 6 or claim 7 wherein (i) b is 0, or (ii) a and d are 0 and b is 1.
9. The use as claimed in any of claims 1 to 4 wherein  $R_1$  is an optionally substituted  $C_1$ - $C_6$  alkyl group,
10. The use as claimed in claim 9 wherein  $R_1$  is  $C_1$ - $C_6$  alkyl substituted by methoxy, ethoxy, methylthio, ethylthio, hydroxy, mercapto, amino, mono- or di-methylamino, mono- or di-ethylamino, fluoro, chloro, bromo, or cyano.
11. The use as claimed in any of claims 1 to 4 wherein in the radical  $R_1$  a is 1 or 0, b is 1, Y is  $-NR^A$ -, and the radical  $-(Alk^4)_d-B$  taken together with  $R_A$  and the nitrogen to which they are attached form an optionally substituted piperidinyl, morpholinyl or piperazinyl ring.
12. The use as claimed in claim 11 wherein the said ring is substituted by hydroxy, mercapto, methoxy, ethoxy, methylthio, ethylthio, amino, mono- or dimethyl amino, mono- or diethyl amino, nitro, or cyano, and in the case of a piperazinyl ring, the second ring nitrogen is optionally substituted by methyl or ethyl.

13. The use as claimed in any of claims 1 to 4 wherein  $R_1$  is hydrogen; chloro; phenyl; phenyl substituted by chloro, bromo, hydroxy, methyl; 2- or 3 thienyl; 3, 5-dimethylisoxazolyl; cyclohexyloxy; and cyclopentyloxy;
14. The use as claimed in any of the preceding claims wherein  $n$  is 0.
15. The use as claimed in any of claims 1 to 13 wherein  $n$  is 1 and Alk is  $-\text{CH}_2-$ ,  $-\text{CH}_2\text{CH}_2-$ ,  $-\text{CH}_2\text{CH}(\text{CH}_3)-$ , or  $\text{CH}_2\text{CH}_2\text{CH}_2-$ .
16. The use as claimed in any of the preceding claims wherein each of  $p$ ,  $r$  and  $s$  is 0, and  $Z$  is hydrogen.
17. The use as claimed in any of claims 1 to 15 wherein  $p$ ,  $r$  and  $s$  are each 0, and  $Z$  is an optionally substituted phenyl, cyclohexyl, pyridyl, morpholino, piperidiny, or piperazyl ring..
18. The use as claimed in any of claims 1 to 15 wherein  $p$  and/or  $s$  is 1 and  $r$  is 0, such that  $Z$  is linked to ring A by an alkylene radical
19. The use as claimed in any of claims 1 to 15 wherein each of  $p$ ,  $r$ , and  $s$  is 1, such that  $Z$  is linked to  $\text{Ar}^1$  by an alkylene radical which is interrupted by the hetero atom-containing  $X$  radical.
20. The use as claimed in any of claims 1 to 15 wherein  $p$  and  $s$  are 0 and  $r$  is 1, such that  $Z$  is linked to  $\text{Ar}^1$  via the hetero atom-containing  $X$  radical.
21. The use as claimed in any of claims 1 to 15 wherein  $p$  is 0,  $r$  is 1, and  $X$  is a sulfonamide radical  $-\text{NR}^{\text{A}}\text{SO}_2-$  or a carboxamide radical  $-\text{NR}^{\text{A}}\text{C}(=\text{O})-$ , wherein  $\text{R}^{\text{A}}$  is hydrogen or a  $(\text{C}_1-\text{C}_6)$ alkyl group, with the N atom linked to the ring A.
22. The use as claimed in claim 21 wherein  $s$  is 1 and  $Z$  is hydrogen.

23. The use as claimed in claim 21 wherein s is 0 and Z is an optionally substituted carbocyclic or heterocyclic ring.
24. The use as claimed in claim 23 wherein Z is optionally substituted phenyl.
25. The use as claimed in any of the preceding claims wherein R is isopropyl.
26. A method of treatment of diseases or conditions mediated by excessive or inappropriate CDK2 activity in mammals, particularly humans, which method comprises administering to the mammal an amount of a compound of formula (I) as defined in any of the preceding claims, or a salt, hydrate or solvate thereof, effective to inhibit said CDK2 activity.
27. A compound of formula (I) as defined in any of claims 1 to 25, or a salt hydrate or solvate thereof, for use in human or veterinary medicine, particularly in the treatment of diseases or conditions mediated by excessive or inappropriate CDK2 activity.
28. The use as claimed in any of claims 1 to 25, a method of treatment as claimed in claim 26, or a compound for use as claimed in claim 27 wherein the CDK activity is associated with cancer, psoriasis or restenosis.

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